REMARKS

Claims 1, 2, 7-12, 14-24 and 27-41 are pending in this application. Claims 1 and 27 are the only independent claims.

The Amendments to and Listing of the Claims have been previously submitted in the response filed on May 27, 2010. As explained in that response, the amendments are supported by the Specification and claims as originally filed and do not introduce any new matter. Thus, entry of the amendments is respectfully requested.

Claim rejections – 35 U.S.C. § 103

Claims 1-3, 7-9, 11, 12, 14-24 and 27-41 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0107149 ("'149 application") in view of U.S. Patent No. 6,099,683 ("'863 patent").

In the Advisory Action, the Examiner states that "the combination of the prior art continues to obviate the instant claims because the '149 application discloses fast dissolving tablets [films] that are administered orally and dissolve instantly in the mouth [0158]," "the '863 patent discloses thin oral tablets comprising a combination of cholinergic substances that dissolves quickly," and that "it would have been obvious to incorporate the drugs of the '863 into the film of the '143 since both applications solve the same problem of fast oral drug delivery." It remains the position of the Examiner that the prior art combination would inherently achieve the claimed dissolution profile, because the "combination comprises the same components (drug(s) and auxiliaries) combined in the same way (thin films with a thickness of 0.05-1 mm) for similar deliver (buccally) to solve the same problem (cognitive disorders)." In addition, the Examiner states that "since the claims do not specify what an effective [plasma] level is, any plasma level would meet this limitation."

All words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). Also see MPEP 2143.03. Applicants may rebut a *prima facie* case of obviousness by a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The

principle applies most often to the less predictable fields, where minor changes in a product or process may yield substantially different results. See *In re Soni*, 54 F.3d 746 at 750 (Fed. Cir. 1995). Also see MPEP 2145.

Claim 1 is directed to a film-shaped medicament for buccal administration of galanthamine or a salt or derivative thereof. The medicament contains one or more cholinergic active substances selected from the group consisting of galanthamine, pharmaceutically acceptable salts of galanthamine, galanthamine derivatives and their pharmaceutically acceptable salts. The medicament is soluble in aqueous media and/or rapidly disintegrating in aqueous media, but is not mucoadhesive. The medicament has a specified dissolution profile, i.e., within thirty minutes after buccal administration, the medicament releases such an amount of the cholinergic active substance(s) contained therein to the oral cavity that an **effective plasma level** is achieved. Although not specified in the claim, the meaning of "effective plasma level" is apparent to those skilled in the art, particularly in view of the disclosure in the specification, that the effective plasma level refers to approx. 10 to 25 ng/ml. See, e.g., paras. [0013], [0017] and [0019] in the present application published as US 2007/0190117. As described in the specification, the presently claimed film-shaped medicament has achieved unexpected superior results, i.e., it has met an unmet need for a fast release dosage form of galanthamine that affords rapid onset of action to achieve the effective plasma level without the occurrence of unacceptable peripheral, especially gastrointestinal and cardiovascular, side effects. See paras. [0013]-[0019].

Applicants respectfully submit that claim 1 and its dependent claims are not *prima facie* obvious, because the cited prior art did not teach the combination of all elements recited in claim 1, particularly the combination of those underlined above. Even assuming claim 1 is *prima facie* obvious, which Applicants strongly disagree, the *prima facie* case is rebutted by the unexpected superior results achieved by the claimed invention.

Contrary to the Examiner's believe, Applicants respectfully submit that the '149 application is not an appropriate primary reference, because it does not teach or suggest a film-shaped medicament that embodies most, if not all, of the properties recited in the present claims . In order to arrive at the subject matter of the presently claimed invention, several selections or modifications must be made based on the disclosure of the '149 application, which include those outlined in detail below.

First, the presently claimed invention is directed to film-shaped medicaments that have a specified dissolution profile, i.e., within thirty minutes after buccal administration, the medicaments release such an amount of the cholinergic active substance(s) contained therein to the oral cavity that an effective plasma level is achieved. The '149 application does not teach any dissolution profile based on effective plasma level of the active ingredient, let alone the one recited in the present claims. According to the '149 application, the thin films can have various drug release profiles, e.g., immediate, delayed, sustained or sequential release profiles. See e.g., paragraphs [0090] to [0095]. The disclosed films that dissolve instantly upon contact with saliva do not inherently represent film-shaped medicaments that release such an amount of the cholinergic active substance(s) contained therein to the oral cavity that an effective plasma level is achieved within thirty minutes after buccal administration, because the dissolution profile is affected by factors not taught or suggested by the '149 application, such as the type of the cholinergic active substance(s), the mucoadhesivity of the film, etc. The Examiner has not provided any evidence to support his inherency statement, because as disclosed in the '149 application and also well known in the art, thin films with the same thickness delivered by the same route can have totally different dissolution profiles. In view of the '149 application, particularly its lack of disclosure of any particular dissolution profile based on effective plasma level of the active ingredient, one skilled in the art could not have possibly been motivated to make and use thin films having the dissolution profile as that recited in the present claims.

Second, the presently claimed invention is directed to film-shaped medicaments that are NOT mucoadhesive. Nowhere does the '149 application disclose that its films are NOT mucoadhesive. Instead, the '149 application discloses that mucoadhesive compositions are particularly useful for its films (paragraph [0155]), that the films will desirably adhere to the oral cavity (paragraph [0156]) or are designed to adhere to the buccal cavity and tongue (paragraph [0094]). Such disclosure teaches away and provides no motivation for one skilled in the art to use films that are NOT mucoadhesive for the presently claimed invention.

Third, the presently claimed invention is directed to buccal administration. However, the '149 application discloses films that can be used for many different routes of administration, such as buccal, gingival, and sublingual applications (paragraph [0093]) and administration to any of several body surfaces, such as oral, anal, vaginal, ophthalmological, the surface of a

wound, skin surface, etc.(para. [0154]). The '149 application provided no specific motivation for one skilled in the art to choose, among all of the disclosed administration routes, buccal administration for the presently claimed invention.

Fourth, the presently claimed invention is directed to film-shaped medicaments for buccal administration of galanthamine or salts or derivatives thereof. Nowhere does the '149 application disclose galanthamine or salts or derivatives thereof. Instead, the '149 application provides a laundry list of hundreds of actives including cholinesterase inhibitors in general that can be delivered by its films (para. [0099]). The '149 application provided no specific motivation for one skilled in the art to choose, among all of the listed actives, cholinesterase inhibitors to be delivered by its films, let alone galanthamine, one of the many cholinesterase inhibitors known in the art. See, e.g., http://en.wikipedia.org/wiki/Cholinesterase_inhibitors.

Because at least four different selections or modifications as those discussed above must be made out of the disclosure of the '149 application, this reference cannot be used as an appropriate primary reference to show obviousness of the presently claimed invention. Thus, the combination of the '149 application with the '863 patent does not render the presently claims obvious.

Even assuming the '149 application is an appropriate primary reference, which Applicants strongly disagree, Applicants respectfully submit it would NOT have been obvious to incorporate the drugs of the '863 patent, i.e., galanthamine hydrobromide, into any immediate release film of the '143 for buccal administration of galanthamine, because of the known side effect associated with the oral administration of fast release dosage forms of galanthamine. As discussed in the specification, one skilled in the art would have been discouraged from using a rapid release film-shaped formulation for buccal administration of galanthamine, because such formulation would have a faster onset of action in the oral cavity than the tablets that deliver galanthamine to the gastrointestinal tract. An even higher plasma concentration galanthamine, thus more severe side effects, would have been expected from the buccal administration of film-shaped formulation for galanthamine. See para. [0019].

Even after the Supreme Court decision in *KSR*, it is still necessary to determine whether there was an apparent reason to combine the known elements in the fashion claimed by applicant and to make the analysis explicit (USPTO Memorandum of May 3, 2007). It is the Applicants'

position that the Examiner has not made explicit analysis on why one skilled in the art would have been motivated to make the several selections or modifications as those discussed above from the disclosure of the '149 application and to make the suggested combination of the '149 application and the '863 patent in order to arrive at the presently claimed invention. Applicants respectfully submit that the Examiner is improperly using hindsight gained from the present invention to arrive at the claimed invention, particularly in view of the unpredictability of the field of art for fast release dosage form of galanthamine, where rapid onset of action may be associated with the occurrence of unacceptable peripheral, especially gastrointestinal and cardiovascular, side effects.

Accordingly, the presently claimed invention is not *prima facie* obvious in view of the combination of the '149 application and the '863 patent.

Even assuming claim 1 is *prima facie* obvious, which Applicants vehemently disagree, the *prima facie* case is rebutted by the unexpected superior results achieved by the claimed film-shaped medicament, i.e., it affords rapid onset of action to achieve the effective plasma level without the occurrence of unacceptable peripheral, especially gastrointestinal and cardiovascular, side effects. As discussed in detail in the specification, such superior result is completely unexpected. See e.g., para. [0019].

Accordingly, reconsideration and withdrawal of the rejection of claims 1-3, 7-9, 11, 12, 14-24 and 27-41 for being unpatentable over the '149 application in view of the '863 patent are respectfully requested.

Claims 1-3, 7-12, 14-24 and 27-41 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '149 application in view of the '863 patent, and further in view of U.S. Patent No. 5,904,929 ("Uekama").

As discussed above, the '149 application in view of the '863 patent does not render the presently claimed invention *prima facie* obvious. For reasons similar to those discussed in the Amendment previously submitted on December 28, 2009, Uekama does not compensate for the defects of the '149 application in view of the '863 patent.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-3, 7-9, 11, 12, 14-24 and 27-41 for being unpatentable over the '149 application in view of the '863 patent and further in view of Uekama are respectfully requested.

It is respectfully submitted that the present application, including claims 1, 2, 7-12, 14-24 and 27-41, is in condition for allowance and such action is respectfully solicited. Applicants appreciate the effort of the Examiner and look forward to receiving the Notice of Allowance of all pending claims.

Respectfully submitted,

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